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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/832,069 | 04/10/2001 | Marschall S. Runge | D6179CIP | 8710 |

7590 02/05/2004

Benjamin Aaron Adler
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| EXAMINER | |
|---|---|
| GOLDBERG, JEANINE ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 02/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/832,069 | RUNGE ET AL. | |
| | Examin r | Art Unit | |
| | Jeanine A Goldberg | 1634 | |

*-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 6-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 6-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is in response to the papers filed November 25, 2003. Currently, claims 6-9 are pending.

### *Information Disclosure Statement*

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

It is noted that no IDS has been filed and applicants did not respond to the notice.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) in view of either Corral-Debrinski et al (Mutation Research, Vol. 275, pages 169-180, 1992)(referred to

as Corral-Debrinski I) or Corral-Debrinski et al (JAMA, Vol. 266, No. 13, pages 1812-1816, October 1991)(referred to as Corral-Debrinski II) or Berlett et al. (J of Biol. Chem. Vol. 272, No. 33, pages 20313-20316, August 1997).

The instant specification defines "oxidative stress" to refer to pathophysiological effects of reactive oxygen species, such as H2O2, superoxide, peroxynitrate, and other reactive oxygen species (page 25 of the specification).

Yan et al. (herein referred to as Yan) teaches in vivo evidence of the relationship of reactive oxygen species and mitochondrial DNA damage in atherosclerosis. Specifically, Yan teaches assaying both diseased and normal human aortic tissues for DNA damage using a gene-specific quantitative PCR assay. Yan teaches designing primers to amplify a fragment of the human mitochondrial genome and a nuclear fragment within the beta-globin gene. Fresh surgical specimens of normal and atherosclerotic human aorta were immediately frozen in liquid nitrogen. Yan reports that mtDNA damage detected in atherosclerotic tissue was 2 to 5 fold higher than that of human aortic samples without evidence of atherosclerosis. The evidence suggest that the average DNA lesion frequency in the mitochondrial genome was approximately four times higher than that in the nuclear B-globin gene (limitations of Claim 6, 7, 8). Yan teaches that the levels of H2O2 and O2- were assessed using a peroxidase-H2O2 formation assay. The results of Yan suggest that an increase in H2O2 and O2- levels in patients with CAD compared to those without CAD, consistent with a correlation between mtDNA damage and ROS generation. Yan teaches that the data suggest that oxidative mtDNA damage may play a role in atherosclerotic lesion development.

Yan does not specifically teach the measurement of mitochondrial DNA damage by measuring mitochondrial mRNA or protein production, or changes in mitochondrial oxidative phosphorylation or ATP production.

However, Corral-Debrinski I teaches an association of mitochondrial DNA damage with coronary atherosclerotic heart disease. Corral- Debrinski I teaches the H2O2 can react with superoxide to generate hydroxyl radical (OH-) which are extremely reactive (page 170, col. 2). The close proximity of the mtDNA to these reactive molecules in the inner mitochondrial membrane and the deficiency in mtDNA repair systems result in preferential oxidative damage to the mtDNA (page 170, col. 2). Corral-Debrinski I teaches that mtDNA is maternally inherited and mutations accumulate 10-20 times faster in the mtDNA than in comparable nuclear genes (page 170, col. 1). Moreover, as seen in Figure 1, oxidative phosphorylation dysfunction is related to decreased cellular ATP, mitochondrial damage and oxygen radical formation.

Corral-Debrinski II teaches that oxidative physphorylation (OXPHOS) increases oxygen radical generation, damage to mtDNA and reduces adenosine triphosphate synthesis (abstract). A comparison of the mtDNA deletion and OXPHOS transcript levels in normal and ischemic hearts was analyzed and they were increased, supporting the hypothesis that OXPHOS inhibition is associated with increased mitochondrial damage (page 1813, col. 1). Corral-Debrinski II also states OXPHOS transcripts have been seen increased in cancer cells (limitations of Claim 9).

Berlett et al. (herein referred to as Berlett) teaches oxidately modified forms of proteins accumulate during aging, oxidative stress (abstract). As seen in Figure 4,

multiple factors affect ROS accumulation (page 20316). Further, Berlett teaches that "it is our belief that during aging there is a progressive accumulation of errors at the level of DNA that affect any one or ore of the factors that govern the dynamics of protein oxidation and oxidized protein degradation. This leads to a shift in the balance between these processes in favor of oxidized protein accumulation and attendant loss of biological function" (page 20316). Berlett suggests that a multiplicity of factors that govern the balance between protein oxidation and degradation may accumulate. Berlett suggest that contribute to diabetes, Alzheimer' disease in which the accumulation of oxidately modified protein has been demonstrated.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the teachings of Yan directed to collecting tissue, measuring the amount of mitochondrial DNA damage, determining the amount of DNA damage in a nuclear gene and comparing the amounts as an indicator of oxidative stress in an individuals to measure the amount of DNA damage using a correlation between mitochondrial mRNA production, measurement of mitochondrial protein production, measurement of changes in mitochondrial oxidative phosphorylation or measurement of changes in mitochondrial ATP production. The prior art, namesly Corral-Debrinski I and II and Berlett teach correlations between between mitochondrial mRNA production, measurement of mitochondrial protein production, measurement of changes in mitochondrial oxidative phosphorylation or measurement of changes in mitochondrial ATP production and mtDNA damage. For example, Corral-Debrinski I teaches illustrates in Figure 1, oxidative phosphorylation dysfunction is related to

decreased cellular ATP, mitochondrial damage and oxygen radical formation. Corral-Debrinski II teaches that oxidative physphorylation (OXPHOS) increases oxygen radical generation, damage to mtDNA and reduces adenosine triphosphate synthesis (abstract). Berlett teaches that "it is our belief that during aging there is a progressive accumulation of errors at the level of DNA that affect any one or ore of the factors that govern the dynamics of protein oxidation and oxidized protein degradation. This leads to a shift in the balance between these processes in favor of oxidized protein accumulation and attendant loss of biological function" (page 20316). Therefore, the ordinary skilled artisan would have been motivated to have detected mtDNA damage using any particular known indicator for mtDNA damage taught in the art. Any means of determining mtDNA damage indirectly which is correlative with measurement of mtDNA damage would have been obvious to the ordinary artisan at the time the invention was made.

***Conclusion***

3. **Claims 6-9 are rejected.**

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571)272-0507

J. Goldberg

**Jeanine Goldberg**
**Patent Examiner**
January 30, 2004